

Potential roles of microRNAs and ROS in colorectal cancer: diagnostic biomarkers and therapeutic targets

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ABSTRACT

As one of the most commonly diagnosed cancers worldwide, colorectal adenocarcinoma often occurs sporadically in individuals aged 50 or above and there is an increase among younger patients under 50. Routine screenings are recommended for this age group to improve early detection. The multifactorial etiology of colorectal cancer consists of both genetic and epigenetic factors. Recently, studies have shown that the development and progression of colorectal cancer can be attributed to aberrant expression of microRNA. Reactive oxygen species (ROS) that play a key role in cancer cell survival, can also lead to carcinogenesis and cancer exacerbations. Given the rapid accumulating knowledge in the field, an updated review regarding microRNA and ROS in colorectal cancer is necessary. An extensive literature search has been conducted in PubMed/Medline databases to review the roles of microRNAs and ROS in colorectal cancer. Unique microRNA expression in tumor tissue, peripheral blood, and fecal samples from patients with colorectal cancer is outlined. Therapeutic approaches focusing on microRNA and ROS in colorectal cancer treatment is also delineated. This review aims to summarize the newest knowledge on the pathogenesis of colorectal cancer in the hopes of discovering novel diagnostic biomarkers and therapeutic techniques.

INTRODUCTION

Over one million new cases of colorectal cancer are identified annually, making it the third most common cancer worldwide [1]. It is largely diagnosed in individuals older than 50 years of age. Thus, standard colonoscopy is recommended starting at the age of 50 to improve early screening and detection [2]. The multifactorial etiology of colorectal cancer consists of both genetic and epigenetic factors. The hereditary syndromes comprise familial adenomatous polyposis, Lynch syndrome (hereditary nonpolyposis colon cancer), MYH-associated polyposis, and juvenile polyposis. Inflammatory bowel disease is also considered a risk factor [3, 4]. Moreover, inappropriate diets and lifestyles are known to associate with increased colorectal cancer incidence. Some risk factors include high intake of red meat/processed food, heavy alcohol

consumption, obesity, smoking, and physical inactivity. It is suggested that the development of colorectal cancer can be prevented by regular exercise and proper diets [5, 6]. The progression of normal colonic mucosa to invasive colorectal cancer requires multiple steps of molecular alterations. The estimated time interval of malignant transformation from normal mucosa to adenomatous polyp and invasive adenocarcinoma is 5-10 years [7]. Five year survival rates for Tumor Node Metastasis (TNM) stages I to IV colorectal cancer are 90%, 80%, 60%, and 8%, respectively [8].

MicroRNA is encoded within the genomes of a variety of eukaryotes, including over 2,500 human mature microRNA sequences in the miRBase database [9-11]. MicroRNAs are evolutionarily conserved, single-stranded noncoding RNA molecules of 19-24 nucleotides, which can suppress gene expression at posttranscriptional levels. MicroRNAs concurrently modulate the expression

Table 1: Dysregulated microRNAs in tumor tissues in patients with colorectal cancer

Dysregulation	Number of studies	microRNAs and references
Upregulated	17	miR-21[44, 45, 64, 65, 71, 75-79, 82, 84, 116-120]
	12	miR-31[45, 64-71, 77, 78, 116]
	9	miR-135b[45, 65, 70, 71, 77, 83, 93, 116, 121]
	8	miR-20a[66, 71, 75, 76, 78, 79, 94, 95]; miR-183[45, 66, 67, 70, 71, 77, 78, 116]
	7	miR-18a[66, 70, 78, 95, 121-123]
	6	miR-19a[71, 77, 78, 95, 116, 121]; miR-96[65, 70, 77, 78, 93, 116]; miR-181b[76, 78, 79, 117, 124, 125]
	5	miR-92[66, 67, 69, 77, 94]; miR-106a[75-79]; miR-203[67, 76-79]
	4	miR-17[67, 71, 95, 122]; miR-17-5p[66, 75, 77, 78]; miR-19b[71, 78, 95]; miR-20[67, 77, 116, 126]; miR-25[67, 77, 78, 122]; miR-182[70, 71, 77, 78]; miR-200c[69, 77, 124, 125]; miR-224[70, 77, 78, 121]
	3	miR-29a[77, 78, 120]; miR-93[67, 71, 78]; miR-106b[78, 121, 122]; miR-130b[71, 77, 78]; miR-142-3p[69, 71, 77]; miR-191[75, 77, 125]; miR-221[71, 75, 127];
	2	miR-15a[71, 77]; miR-15b[77, 125]; miR-17-3p[70, 77]; miR-29b[78, 120]; miR-32[70, 75]; miR-34a[77, 78]; miR-92a[44, 122]; miR-95[77, 78]; miR-98[71, 77]; miR-105[77, 93]; miR-107[75, 77]; miR-135a[67, 77]; miR-148a[71, 77]; miR-182*[70, 77]; miR-188[69, 70]; miR-200a*[77, 94]; miR-210[69, 77]; miR-223[67, 75]; miR-301b[45, 121]; miR-320[77, 94]; miR-324-5p[71, 77]; miR-424[121]; miR-493[45, 93]; miR-513a-5p[82, 120]; miR-552[70, 93]; miR-584[70, 93]; miR-let-7g[77, 124]
Downregulated	1	miR-1[120]; miR-7[93]; miR-10a[77]; miR-19b-1[95]; miR-24-1[75]; miR-27a[77]; miR-29b-2[75]; miR-30b[120]; miR-30c[75]; miR-33[70]; miR-92a-1[95]; miR-103[77]; miR-122a[77]; miR-128a[77]; miR-128b[75]; miR-133b[67]; miR-134[77]; miR-135b*[83]; miR-141[77]; miR-142-5p[77]; miR-145[120]; miR-146[77]; miR-147[77]; miR-150[75]; miR-151[77]; miR-154*[77]; miR-155[75]; miR-181a[77]; miR-181c[77]; miR-183*[83]; miR-186[77]; miR-191*[94]; miR-194[77]; miR-197[77]; miR-199a-3p[120]; miR-200a[69]; miR-200b[77]; miR-213[77]; miR-214[71]; miR-215[77]; miR-216[77]; miR-219[77]; miR-222[77]; miR-296-3p[93]; miR-301[77]; miR-302a[94]; miR-330[77]; miR-338[77]; miR-338-3p[120]; miR-339[77]; miR-362[45]; miR-370[77]; miR-373[77]; miR-374[77]; miR-382[45]; miR-432*[94]; miR-451[120]; miR-483-3p[93]; miR-492[94]; miR-494[82]; miR-500[82]; miR-503[70]; miR-510[94]; miR-512-5p[94]; miR-513[94]; miR-513b[82]; miR-513c[82]; miR-526c[94]; miR-527[94]; miR-542-5p[70]; miR-549[93]; miR-582-5p[71]; miR-592[93]; miR-622[128]; miR-708[45]; miR-766[83]; miR-886[45]; miR-892b[82]; miR-938[128]; miR-1238[128]; miR-1247[93]; miR-1260[120]; miR-1269[93]; miR-1290[128]; miR-1827[93]; miR-3144-3p[93]; miR-3180-3p[93]; miR-4326[93]; miR-HS-29[70]; miR-HS-287[70]; miR-let-7f[71]
	14	miR-145[45, 64, 66-69, 77, 78, 82, 83, 93, 94, 116, 129]
	10	miR-143[64, 66, 67, 69, 78, 82-84, 129, 130]
	8	miR-1[45, 70, 71, 78, 82, 93, 128, 131]
	7	miR-195[77, 78, 82, 83, 93, 105, 132]
	6	miR-378[70, 78, 82, 83, 93, 121]
	5	miR-133a[45, 70, 71, 78, 82]; miR-133b[45, 82, 83, 116, 128]; miR-139-5p[45, 71, 82, 83, 93]; miR-192[67, 69, 82, 83, 133]; miR-215[67, 71, 82, 83, 133]
	4	miR-30a-3p[70, 77, 78, 116]; miR-375[70, 71, 83, 134]; miR-422a[71, 78, 83, 93]
	3	miR-9[45, 70, 72]; miR-10b[70, 78, 82]; miR-16[67, 83, 135]; miR-26b[67, 83, 94]; miR-30b[82, 83, 94]; miR-30c[78, 82, 83]; miR-138[45, 83, 128]; miR-139[70, 77, 78]; miR-194[82, 83, 133]; miR-363[70, 82, 93]; miR-378*[82, 83, 121]; miR-490-3p[82, 93, 128]; miR-497[70, 78, 82]; miR-let-7a[67, 136, 137]
	2	miR-9*[70, 82]; miR-28-3p[71, 120]; miR-30a*[82, 83]; miR-30a-5p[70, 78]; miR-30e[82, 83]; miR-101[83, 94]; miR-125b[69, 77]; miR-137[70, 82]; miR-149[71, 77]; miR-150[120, 138]; miR-192*[82, 83]; miR-204[45, 71]; miR-320a[139]; miR-328[70, 116]; miR-365[82, 140]; miR-486-5p[83, 93]; miR-551b[70, 93]; miR-598[82, 83]; miR-642[70, 71];
	1	miR-1[120]; miR-7-1*[82]; miR-20b[70]; miR-22[141]; miR-23b[120]; miR-24-1*[82]; miR-26a[83]; miR-27b[82]; miR-28-5p[82]; miR-30a[82]; miR-30e*[83]; miR-31[82]; miR-31*[82]; miR-34c[142]; miR-34a[142]; miR-99a[83]; miR-100[83]; miR-113; miR-122[82]; miR-124a[116]; miR-125a[78]; miR-126[143]; miR-127-3p[83]; miR-129[116]; miR-133[117]; miR-139-3p[120]; miR-140-5p[83]; miR-143*[82]; miR-144[82]; miR-144*[83]; miR-147[70]; miR-186[83]; miR-190[83]; miR-191[67]; miR-193b[69]; miR-196a[67]; miR-200b[83]; miR-203[118]; miR-212[69]; miR-214[69]; miR-218[82]; miR-299-5p[71]; miR-342-3p[83]; miR-345[144]; miR-362-3p[82]; miR-378c[93]; miR-381[145]; miR-383[93]; miR-411[83]; miR-422b[78]; miR-424[120]; miR-451[83]; miR-455[94]; miR-484[94]; miR-485-3p[71]; miR-486[70]; miR-506[146]; miR-511[70]; miR-582-5p[82]; miR-590-5p[82]; miR-622[147]; miR-628-3p[93]; miR-628-5p[93]; miR-636[83]; miR-650[70]; miR-885-5p[45]; miR-886-3p[71]; miR-892b[120]; miR-1288[120]; miR-1297[93]; miR-1305[120]; miR-3151[93]; miR-3163[93]; miR-3622a-5p[93]; miR-3656[93]

Table 2: Dysregulated microRNAs in sera or plasma samples in patients with colorectal cancer

Source	Dysregulation	Number of studies	microRNAs and references
Sera	Upregulated	3	miR-92a[85, 148, 149]; miR-221[149-151]
		2	miR-21[45, 152]; miR-210[85, 149]
		1	miR-19a[149]; miR-22*[149]; miR-24[149]; miR-92[153]; miR-125a-5p[149]; miR-134[150]; miR-141[154]; miR-146a[150]; miR-320a[85]; miR-376a[149]; miR-378[85]; miR-423-5p[85]; let-7e[149]; miR-222[150]; miR-423-5p[85]
	Downregulated	2	miR-143[85, 89]
		1	miR-10a[149]; miR-103[85]; miR-106a[85]; miR-107[85]; miR-141[149]; miR-145[96]; miR-150[149]; miR-151-5p[85]; miR-188-3p[149]; miR-192[149]; miR-199a-3p[85]; miR-224*[149]; miR-382[85]; miR-425*[149]; miR-495[149]; miR-572[149]; miR-601[149]; miR-720[149]; miR-760[149]; let-7a[149]; let-7d[85]

levels of dozens or more messenger RNA (mRNA), and any given mRNA sequence may be targeted by several different microRNAs [9, 10, 12]. To date, microRNAs have been predicted to target and control the expression of at least 30% of all protein-coding genes, and they participate the regulation of nearly every cellular process studied so far [13]. Specifically, microRNAs appear to be involved in multiple pathophysiological networks and in the pathogenesis of a broad-spectrum of human diseases, including cancer and inflammation [14-21]. The greater stability of microRNAs relative to mRNAs supports the use and development of microRNAs as promising targets in diagnostic and therapeutic applications of various diseases [22]. Indeed, plasma microRNAs have been used for early detection of cancer such as colorectal cancer, which is essential in improving prognosis [23, 24]. MicroRNAs also demonstrate high sensitivity and specificity in cancer diagnosis, further confirming their potential as biomarkers [24].

Over the past 15 years, researchers have identified distinct aberrant microRNA expression profiles in tumor tissue, peripheral blood, and fecal samples of colorectal cancer patients, suggesting the critical roles that microRNAs play in the pathogenesis of oncogenic transformation. In addition, reactive oxygen species (ROS), serving as important cell signaling molecules, are involved in the progression of cancer cells as well as in microRNA expression. Elevated ROS levels and accumulated mutations due to oxidative DNA damage are prominent in cancer cells, favoring the survival and growth of cancer [25, 26]. Particularly in colorectal cancer, the irritated intestines and altered gut microbiota composition can contribute to additional production of intestinal ROS. Indeed, a marked increase in oxidative stress markers such as 8-oxodG (an indicator of DNA oxidation) was observed in colorectal cancer patients, suggesting the potential role of ROS in colorectal cancer [27]. Growing evidence from cancer studies has revealed that microRNA expression alters in response to ROS exposure [28]. In addition to the ROS-mediated tumor progression, it is likely that ROS are also involved in the microRNA-related mechanisms of promoting colorectal carcinogenesis. Understanding the interplay between microRNAs and ROS is paramount

since both have been shown to be dysregulated in cancers. Herein, the review focuses on the current understanding of microRNAs and ROS in the pathogenesis and potential diagnostic and therapeutic implication in colorectal cancer.

ABERRANT MICRORNA PROFILES AND ROS LEVELS IN COLORECTAL CANCER

MicroRNA profiles in colorectal tissues, plasma, and stool samples

Nearly 400 dysregulated microRNAs have been identified in colorectal cancer in the past decade, yet minimal consistency of microRNA expression profile is reported. Despite the striking potential of microRNAs as biomarkers of cancer, the transition of microRNAs from bench to clinical use remains challenging as the detection techniques including the commonly used qRT-PCR are needed to be optimized. For example, the selection of suitable reference genes for data normalization in the qRT-PCR analysis is highly subjective, which may lead to inconsistency among different studies. The intrinsic properties of microRNAs, such as a high degree of sequence similarity within the same family, tissue-specific expression, and small-quantity, also cause certain limitations of these detection methods [24]. In addition, by far a considerable amount of results in the literature is derived from retrospective cohorts, thereby limiting the prognostic significance of microRNAs and possibly contributing to some inconsistent results.

As listed in Table 1, aberrantly elevated microRNAs have been frequently found in cancerous colon tissues. Overexpressed miR-31 is commonly observed in colorectal tumor tissues, and is associated with tumor prognosis [29]. Given the variable and diverse anatomic locations of colorectal cancer, treatment management, tissue processing, cohorts of normal control, and analytical methods, which all might impact results, it is not surprising that the findings are not consistent. Similarly, there is no established general consensus on the normalization of

Table 3: Dysregulated microRNAs in fecal samples in patients with colorectal cancer

Source	Dysregulation	Number of studies	microRNAs and references
Feces	Upregulated	4	miR-21[44, 86, 155, 156]
		2	miR-106a[155, 157]
		1	miR-18a[156]; miR-19a[156]; miR-20a[86]; miR-92[86]; miR-92a[44]; miR-96[86]; miR-106a[86]; miR-135a[156]; miR-135b[156]; miR-144[158]; miR-203[86]; miR-326[86]
	Downregulated	2	miR-143[86, 87]; miR-145[86, 87]
		1	miR-16[86]; miR-125b[86]; miR-126[86]; miR-320[86]; miR-484-5p[86]

circulating microRNAs despite the distinct microRNA expression profiles observed in sera or plasma of patients with colorectal cancer (Table 2). Among these highly expressed circulating microRNAs, several are found in the peripheral blood mononuclear cells and others are known to be secreted by the tumor tissues. Indeed, miR-21 is abundantly present in colorectal tumor tissues and is secreted to the circulation. Levels of miR-21 in the serum sample decrease after surgical removal of primary tumor, suggesting the need of establishing an in-depth evaluation of circulating microRNAs for diagnosis [30]. Fecal occult blood testing is a useful option for early detection, but the sensitivity is low [31]. So far, less than 40% of colorectal cancers are detected in the early stage [32]. Therefore, there is a strong demand for the development of accurate and noninvasive markers. Given the continuous releasing of colonic epithelia into the lumen, detecting microRNA in fecal samples from colorectal cancer patients is a promising tool for the early diagnosis of colorectal cancer. As listed in Table 3, altered microRNA expression profiles are found in stool samples from patients with colorectal cancer. Among them, miR-21, miR-106a, miR-143, and miR-145, have been found by at least two independent groups.

ROS in colorectal cancer

ROS, including superoxide ($O_2^{\cdot-}$), hydroxyl radical ($\cdot OH$) and hydrogen peroxide (H_2O_2), are generated under physiological conditions and serve as important mediators in multiple cell signaling pathways. Despite their importance, excessive ROS can oxidize major cellular components (e.g., DNA, lipids, and proteins), resulting in irreversible damages [33]. Normally, the cellular levels of ROS are carefully monitored by the body's natural antioxidant defense system in order to maintain redox homeostasis. When such homeostasis is disrupted (termed oxidative stress), either due to ROS overproduction or compromised antioxidant function, it can give rise to pathological conditions that ultimately leads to diseases [34, 35]. Compared to normal cells, the basal level of ROS has been shown to elevate in cancer cells, which is mainly attributed to increased metabolic activity and altered cellular signaling [26]. Originating from the epithelium in the intestine, colorectal cancer cells have a high metabolic rate and often divide rapidly, potentially

causing DNA oxidation [27]. These ROS-induced genetic mutations as well as transcription factor modulations (e.g., hypoxia inducible factor-1) are crucial in the regulation of gene expression relative to cancer cell survival, growth, invasion, and metastasis, contributing to all three stages of carcinogenesis (initiation, promotion and progression) [25, 27]. Cancer cells are normally accompanied with strong antioxidant defenses, generating a powerful ROS scavenging capacity that can adapt to a highly oxidized environment and avoid apoptosis [25, 26]. Sustained and excessive ROS promote oncogenic activity and genomic instability, contributing to carcinogenesis [28]. The association between colorectal cancer and oxidative stress has been identified in the past decades. Additionally, the increased levels of oxidative stress biomarkers, such as 8-oxodG in DNA, suggest that the ROS are markedly elevated in the whole blood of patients with colorectal cancer [27].

In a study of primary rat colonocytes, Oberreuther-Moschner *et al.* observed that cells from the lower aspect of colon crypts, mostly proliferating cells, are more sensitive to ROS- H_2O_2 damage [36]. The stem/progenitor cells' capacities of self-renewal and differentiation are also largely influenced by varied redox environments. Therefore, these cells are putative targets for colon cancer treatment [27]. Recent efforts have focused on the development of effective therapies that combat cancer cells, by facilitating the induction of apoptosis *via* drug-induced ROS. These methods include various chemotherapeutic/anti-cancer drugs [25]. In contrast, lowering oxidative stress or increasing the total antioxidant capacity through a vegetable- and fruit-rich diet has shown to decrease the potential risk of colorectal cancer. Western diets that commonly consist of red meat, which contains high quantity of iron, are not favorable since heme iron promotes cell transformation and oxidative DNA damage by exacerbating oxidative stress in the body [25]. Acting as a double-edge sword, intracellular ROS levels play critical roles in determination of the fate for cancer cells. As such, the survival of cancer cells in the presence of either very high or low ROS levels is not favorable, and therapies targeting redox disruption should be carried out with cautions [33].

Table 4: Colorectal cancer-associated microRNAs and their validated gene targets

	MicroRNA	Confirmed gene target	References
Oncogene	miR-9	E-cadherin	[159]
	miR-17	RND3	[126]
	miR-18a	ATM	[160]
	miR-19a	TF	[161]
	miR-21	PDCD4, PTEN, RASA1, Rho B, TGFβR2	[54, 56-63]
	miR-26b	E3 ubiquitin ligase DIP1	[162]
	miR-30	GRP78	[163]
	miR-31	RASA1	[73]
	miR-32	PTEN	[164]
			[44, 165-169]
	miR-92a	PTEN	[170]
	miR-95	SNX1	[171, 172]
	miR-106a	RB1, TGFβR2	[80, 81]
	miR-135a	Metastasis suppressor 1	[173]
	miR-191	C/EBPβ	[174]
	miR-214	FGFR1	[175]
	miR-224	p21, MBD2, PHLPP1, PHLPP2, SMAD4	[176-179]
	miR-499-5p	FOXO4, PDCD4	[180]
	miR-675	RB	[181]
Tumor suppressor	miR-7	YY1	[182]
	miR-16	CDK6, cyclin D1, survivin	[135, 183]
	miR-22	p21	[184]
	miR-28-5p	CCND1, HOXB3	[185]
	miR-33a	Pim-1	[186]
	miR-34	Axin2, snail1	[187, 188]
	miR-34a	PDGFRα, LDHA, MDM4, SIRT1	[44, 165-167, 169]
	miR-93	CCNB1, ERBB2, Smad 7	[189 , 190]
	miR-100	Lgr5	[191]
	miR-124	iASPP, STAT3	[114, 192]
	miR-126	CXCR4, phosphatidylinositol 3-kinase	[193-195]
	miR-127	BCL6	[196]
	miR-133b	TBPL1	[197]
	miR-139	RAP1B, IGF-IR	[198, 199]
	miR-139-5p	IRS1, Notch1,	[200]
	miR-143	DNMT3A, HK2, IGF-IR, MACC1	[89-92]
	miR-144	ROCK 1	[201]
	miR-145	DFF45, FLI1, IRS1, N-RAS, PAK4, p70S6K1, paxillin, STAT1, YES	[96, 98-103]
	miR-148a, b	Bcl-2, CCK2R	[202, 203]
	miR-181a	GRP78	[163]
	miR-199a-5p		
	miR-195	Bcl-2	[105]
	miR-203	Hakai	[204]
	miR-204	TFAM	[205]
	miR-215	DTL	[206]
	miR-218-5p	BMI1	[207]
	miR-221	MBD2	[178]
	miR-320a	β-catenin, neuropilin 1	[139, 208]
	miR-339-5p	PRL-1	[209]
	miR-342	DNMT1	[210]
	miR-362-3p	E2F1, PTPN1, USF2	[211]
	miR-365	Bcl-2, cyclin D1	[140]
	miR-375	PIK3CA	[212]
	miR-381	LRH-1	[145]
	miR-455	RAF1	[213]
	miR-497	IGF-IR	[214]
	miR-506	EZH2	[146]
	miR-622	K-Ras	[147]
	miR-627	JMJD1A	[215]
	miR-1915	Bcl-2	[216]
	Let-7	K-Ras, MMP11, PBX3	[217]

Abbreviation: ARL2, ADP-ribosylation factor-like protein 2; ATM, ataxia telangiectasia mutated; BIM, BCL-2-interacting mediator of cell death; CCK2R, cholecystokinin-2 receptor; CCND1, cyclin D1; COX-2, cyclooxygenase-2; DAPK, death-associated protein kinase; DFF45, DNA fragmentation factor-45; DNMT1, DNA methyltransferase 1; DNMT3A, DNA methyltransferase 3A; DTL, denticleless protein homolog; FGFR1, fibroblast growth factor receptor 1; FLI1, friend leukemia virus integration 1; HIF-2 α , hypoxia-inducible factor-2 α ; HK2, hexokinase 2; iASPP, apoptosis-stimulating protein of p53; IGF-IR, type I insulin-like growth factor receptor; IRS2, insulin receptor substrate 2; LDHA, lactate dehydrogenase A; Lgr5, leucine-rich repeat-containing G protein-coupled receptor 5; LRH-1, liver receptor homologue 1; KLF4, krüppel-like factor 4; K-Ras, Kirsten rat sarcoma; JMJD1A, Jumonji domain containing 1A; MACC1, metastasis-associated in colon cancer-1; MAPK, mitogen-activated protein kinase; NIRF, Np95 ICBP90 ring finger; PDCD4, programmed cell death 4; PHLPP, PH domain leucine-rich-repeats protein phosphatase; PI3K, phosphatidylinositol-3 kinase; PIAS3, the protein inhibitor of activated STAT3; PIK3CD, phosphoinositide 3-kinase catalytic subunit delta; PRL-1, phosphatases of regenerating liver-1; PDGFR α , platelet-derived growth factor receptor α ; PPAR γ , peroxisome proliferation-activated receptor γ ; PTEN, phosphatase and tensin homologue; RAF1, proto-oncogene serine/threonine-protein kinase; RASA1, RAS p21 GTPase activating protein 1; Rho B, ras homolog gene family, member B; ROCK1, Rho-associated coiled-coil containing protein kinase 1; SNX1, sorting nexin 1; TBPL1, TATA-box binding protein like 1; TF, tissue factor; TFAM, mitochondrial transcription factor A; YY1, Yin Yang 1

Interaction of microRNAs and ROS

Since the dysregulation of microRNAs and ROS are both observed in colorectal cancer, it is essential to understand their potential role of interaction in relation to colorectal carcinogenesis and progression. Among those microRNAs presented in our tables, miR-210 overexpression has been shown to increase ROS production in colorectal cancer cells [37, 38]. The augmented ROS can be attributed to compromised mitochondrial activity as miR-210 inhibits mitochondrial iron-sulfur cluster scaffold homologue and the assembly iron-sulfur cluster [37, 39]. MiR-210 also induces ROS generation under hypoxic condition, leading to a poor prognosis in colorectal cancer [37, 38]. Furthermore, Tagscherer *et al.* observed miR-210-induced colorectal cancer apoptosis. However, the roles of elevated ROS and miR-210 levels in the regulation of apoptosis and their biological relevance in colorectal cancer have not been thoroughly elucidated and require further investigation [37]. Additionally, overexpressed miR-141 and miR-200a can modulate oxidative stress by targeting p38 α and potentiate tumor growth [28].

Accumulating studies reveal that ROS can alter the expression of several microRNAs. For example, exogenous H₂O₂ exposure has led to the upregulation of miR-21 while lowered the expressions of miR-27a*, miR-27b*, miR-29b, and miR-328 [28]. It has been shown that ROS regulate microRNA expression through microRNA biogenesis, transcription factors, and epigenetic alterations. In addition, microRNA response can be abrogated when ROS are scavenged [28]. Studies indicated that ROS upregulate miR-21 expression, actively involving in the initiation of cancer metastasis [40, 41]. MiR-21 plays an essential role in many aspects of colorectal carcinogenesis as its upregulation has been found in the tumor tissues, serum, and stool of patients with colorectal cancer (Table 1, 2, 3). Although the targets of miR-21, including several tumor suppressors, have been successfully identified, the continuation of extensive research on this matter is essential to elucidate the diverse mechanisms of miR-21

in the cancer development [42, 43]. It is suggested that one of the potential mechanisms utilized by miR-21 to promote tumorigenesis is through the alteration of cellular ROS levels [43]. In the study of Zhang *et al.*, miR-21 has been shown to suppress SOD3 directly or SOD2 indirectly by reducing TNF- α production, thereby inhibiting the dismutation of O₂⁻ to the less damaging molecule of H₂O₂ [43]. In the miR-21 overexpressing cells that are under irradiation (IR), the accumulated O₂⁻ may be involved in the IR-induced cell transformation. Along with other targets of miR-21, such modulations of ROS levels contribute to the carcinogenesis [43]. Although miR-21-ROS interaction has not been documented in colorectal cancer yet, further research may be necessary to explore towards this direction, and perhaps with other microRNAs, given their tight association with the colorectal cancer.

Certain microRNAs, such as miR-34a, have been shown to inhibit ROS synthesis by silencing the genes that code for mitochondrial complexes and other ROS-producing enzymes, contributing to apoptosis resistance. The restoration of these microRNAs is suggested to sensitize the tumor in response to IR-induced oxidative effects [28]. Clearly, ROS and microRNAs are capable of interacting synergistically or antagonistically to influence the complex and multiphase development of cancer. However, limited effects have been observed in the application of antioxidants or microRNAs in cancer treatment, and the functional consequences of individual microRNA in colorectal cancer patients are still largely unknown. Further exploration on the ROS-microRNAs network may provide powerful therapeutic potential for colorectal cancer as microRNAs can be utilized to enhance ROS-induced apoptosis or alleviate ROS-mediated oxidative stress [28].

MICRORNA AS A POTENTIAL CARCINOGENIC DRIVER

The multifactorial etiology of colorectal cancer involves both genetic and epigenetic alterations of proto-oncogenes and tumor suppressor genes,

which leads to complicated aspects of tumorigenesis, including cell proliferation, apoptosis, genomic stability, angiogenesis, metastasis and chemoresistance. Increasing evidence supports a specific and important role of noncoding genomic sequences, including microRNA in carcinogenesis. MicroRNAs exert various biological functions in tumorigenesis by altering the expression of oncogenes and/or tumor suppressors. MicroRNAs generally regulate gene expression by binding to the 3' untranslated region (UTR) of their target mRNAs to repress translation [9, 10, 12]. Computational methods play an essential role in predicting proposed targets. In the past decade, multiple target genes of microRNAs in colorectal carcinogenesis have been proposed, validated, and confirmed in variable signaling pathways (Table 4). Here we focus on the microRNAs with the best evidence as drivers of carcinogenesis.

Oncogenes

miR-21

Oncogenic miR-21 is one of the most extensively studied microRNAs. Its expression is often upregulated in tumor tissue, sera, and stool samples from patients with colorectal cancer [44-46]. Remarkably, serum miR-21 has been shown to be a promising biomarker of colorectal cancer for early detection and prognosis [30]. The expression level of miR-21 is associated with TNM staging, recurrent-free cancer-specific survival, and overall survival [46, 47]. In addition, the expression of miR-21 is decreased after chemotherapy, which is related to tumor response [48]. Several studies have shown that miR-21 overexpression significantly increases the resistance of tumor cells to 5-fluorouracil and radiation in colon cancer cells [49]. Furthermore, the knockdown of miR-21 reversed these effects on tumor cells by increasing the sensitivity to 5-fluorouracil chemotherapy [49, 50]. One study suggests that miR-21 mediates resistance through the regulation of Sprouty 2 protein, a tumor suppressor, which enhances the cytotoxic effect of 5-fluorouracil in colon cancer cells [51]. These findings indicate that targeting miR-21 could enhance the sensitivity of cancer cells to chemoradiotherapy.

MiR-21 participates in many facets of tumorigenesis including cell proliferation, apoptosis, tumor stemness, and invasion [52-55]. Transforming growth factor β receptor 2 (TGF β R2), programmed cell death 4 (PDCD4), Rho B, PTEN, and RAS p21 GTPase activating protein 1 (RASA1) are the validated target genes by miR-21 (Figure 1) [54, 56-63]. MiR-21 overexpression is associated with induction of tumor stemness through the downregulation of TGF β R2 and the augmentation of β -catenin TCF/LEF signaling pathway [54]. As a tumor suppressor, PDCD4 inhibits tumor progression and neoplastic transformation, while miR-21 restrains the functions of PDCD4 by directly

suppressing its expression [57]. MiR-21 also regulates RAS signaling pathway to affect colon cancer cell behaviors *via* direct effect on RASA1 and Rho B (Figure 1) [58, 59]. In addition, miR-21 regulates the biological behavior of human colorectal cancer cells through PTEN/PI-3 K/Akt signaling pathway [60]. Taken together, these findings suggest miR-21 as a carcinogenesis instigator and potential therapeutic target for colon cancer treatment worthy of further investigation.

miR-31

Uniformly elevated expression of miR-31 is also observed in tumor tissue of colorectal cancer patients [64-70]. The expression level of miR-31 is positively correlated with the tumor TNM staging [65, 71]. MiR-31 is involved in cell proliferation and apoptosis by activating RAS signaling pathway through the inhibition of its target gene, RASA1, thereby enhancing cancer cell growth (Figure 1) [72, 73]. Functional analysis has demonstrated that an inhibitor of miR-31 has an anti-tumor effect [74]. Thus, miR-31 may serve as a diagnostic biomarker and a promising therapeutic target in colon cancers.

miR-106a

As an oncogene, miR-106a is upregulated in colorectal cancer, which is also associated with tumor metastasis [75-80]. Retinoblastoma 1 (RB1) and TGF β R2 are validated direct target genes of miR-106a [80, 81]. RB1, an important tumor suppressor gene involved in cell cycle, is directly regulated by miR-106a [81]. In addition, miR-106a is highly expressed in metastatic colon cancer cell lines that can enhance tumor migration and invasion by modifying TGF β R2 directly (Figure 1) [80].

TUMOR SUPPRESSOR GENES

miR-143

As a tumor suppressor, miR-143 is downregulated in tumor tissue, sera, and fecal samples of patients with colorectal cancer [82-87]. Its expression is also decreased in the front-specific tumor invasion in liver metastasis [88]. Reduced expression of miR-143 is associated with aggressive mucinous phenotype and is strongly correlated with clinical stage and nodal metastasis [71, 89]. The augmented postchemotherapy level of miR-143 is thought to be associated with a better prognosis [48].

Hexokinase 2 (HK2), metastasis-associated in colon cancer-1 (MACC1), insulin-like growth factor-I receptor (IGF-IR), KRAS, and DNA methyltransferases 3A (DNMT3A) are the confirmed target genes of miR-143 [89-92]. Studies have shown that HK2 is involved in glucose metabolism in colon cancer cells [90]. MACC1 has been identified to express highly in colorectal cancer cells and promotes tumor metastasis through activating a

metastasis-inducing HGF/MET signaling pathway [91]. MiR-143 plays a role in suppressing colorectal cancer cell growth *via* directly inhibiting KRAS [69]. IGF-IR, a known oncogene, has expression levels that are inversely correlated with miR-143 expression in human tumor tissues (Figure 2). In an IGF-IR-dependent manner, miR-143 overexpression has been shown to boost colorectal cancer chemosensitivity to oxaliplatin treatment [89]. In addition, specific changes in DNA methylation patterns are associated with human cancers. Methylation changes to the genome are controlled by DNA methyltransferases (DNMT). MiR-143 specifically regulates DNMT3A that reflects its role in the regulation of DNA methylation (Figure 2) [92]. Taken together, through modulating multiple targets, miR-143 provokes potent effects on cancer cell growth and tumorigenesis.

miR-145

MiR-145 is a commonly studied tumor suppressor microRNA in colorectal cancer, which is downregulated

in tumor tissue, sera, and fecal samples [29, 83, 87, 93-96]. Its decreased expression is even present in the front-specific tumor invasion in liver metastasis [88]. Similar to miR-143, the increased postchemotherapy level of miR-145 is predictive of a better prognosis [48].

Reduced expression of miR-145 has been observed in the non-mutated adenomatous polyposis coli, suggesting its role in the initiation of colorectal tumor development [97]. PAK4, N-RAS, IRS1, paxillin, FLI1, DFF45, and p70S6K1 are the known recognized targets of miR-145 (Figure 2) [96, 98-105]. PAK4, a subfamily of serine/threonine kinases linked to cell growth, motility, and cytoskeletal dynamics, is greatly involved in oncogenic signaling pathways [101]. Overexpressed miR-145 exerts its anti-tumor function by modulating a target gene, PAK4, which blocks the activation of AKT and ERK1/2 pathways, thus inhibiting tumor growth [101]. In addition, miR-145 also blocks the activation of AKT and ERK1/2 pathways and the expression of HIF-1

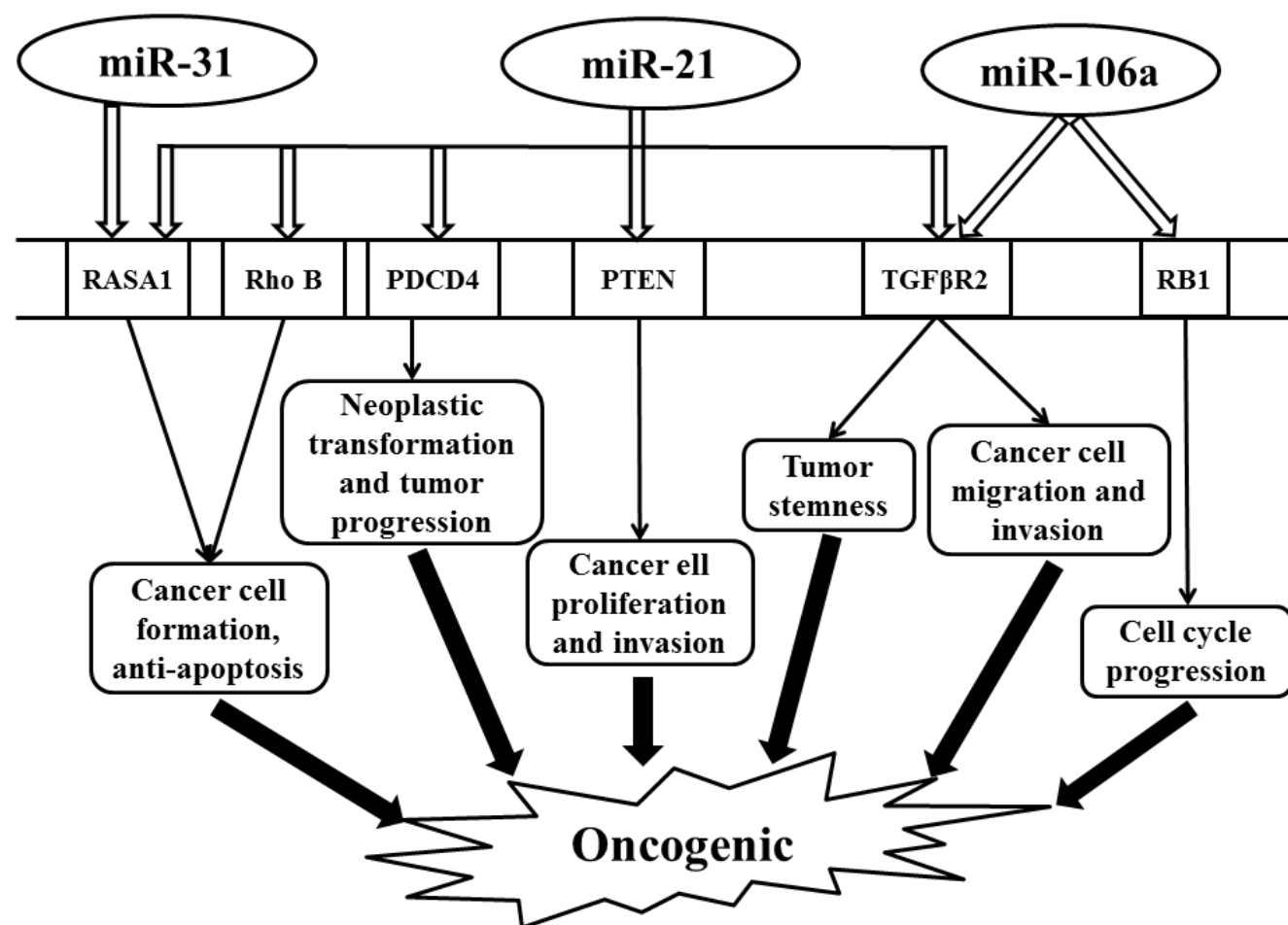


Figure 1: Schematic illustrating the oncogenic effect regulated by miR-31, miR-21, and miR-106a in colorectal cancer. Abbreviations: PDCD4, programmed cell death 4; PTEN, phosphatase and tensin homologue; RASA1, RAS p21 GTPase activating protein 1; RB1, retinoblastoma 1; Rho B, Ras Homolog Family Member B; TGFβR2, transforming growth factor β receptor 2.

and VEGF *via* directly targeting N-RAS and IRS1, leading to the inhibition of tumor growth [96]. Meanwhile, miR-145 is involved in inhibiting cell proliferation, migration, and invasion by targeting paxillin [99]. MiR-145 also regulates the 3'-UTR of Fli-1 mRNA. The downregulation of Fli-1 has a profound effect on the growth of colon cancer [102]. DNA fragmentation factor-45, a direct target by miR-145, plays an essential role in apoptosis, a crucial aspect of tumorigenesis [106]. MiR-145 is a key regulator of intestinal cell differentiation by directly targeting SOX9, a marker of undifferentiated progenitors in the colonic crypts [100]. However, whether SOX9 is oncogenic remains controversial as inactivating mutation of this gene is frequent in colorectal cancer [107]. Indeed, Bastide *et al.* observed the presence of microadenomas in the intestinal epithelium of SOX9-knockout mice. SOX9 acts a regulator of Wnt/beta-catenin pathway and a transcriptional target to maintain intestinal epithelium homeostasis [108]. In addition, SOX9 expression is an important biomarker for the prediction of colorectal cancer relapse [109]. MiR-145 also directly targets catenin δ -1 and contributes largely to oncogenic Wnt/beta-catenin signaling in human colon cancer cells (Figure 2) [104]. Moreover, miR-145 targets p70S6K1 and downregulates HIF-1 and VEGF expression thereby inhibiting tumor growth and angiogenesis [103]. These findings support

miR-145 as an important mediator in tumorigenesis and indicate the potential development of the miR-145-based targeted approach for the treatment of colorectal cancer.

MICRORNAS AS PROMISING THERAPEUTIC TARGETS FOR COLORECTAL CANCER

Exploring the underlying mechanisms that regulate gene expression and the complex signaling pathways is essential in developing novel therapeutics in colorectal cancer treatment. The distinctive ability of microRNAs to target multiple genes and signaling pathways has drawn great attention to their roles as potential innovative therapeutic agents. Generally, microRNA-based therapies include the restoration of downregulated/tumor suppressor microRNA expression or the inhibition of overexpressed/ oncogenic microRNAs [110]. For example, the silencing of miR-135b, in which its upregulation corresponds to colorectal tumor progression, reduces the number and size of tumors in a mouse model with no obvious signs of toxicity [111]. In a mouse model of colon carcinoma, intact tumor suppressor miR-145 molecules that are successfully delivered into xenograft tumors result in profound anti-tumor effects by increasing apoptosis and reducing tumor size [98]. Despite functioning as oncogenes or tumor suppressors, microRNAs are also involved in immune

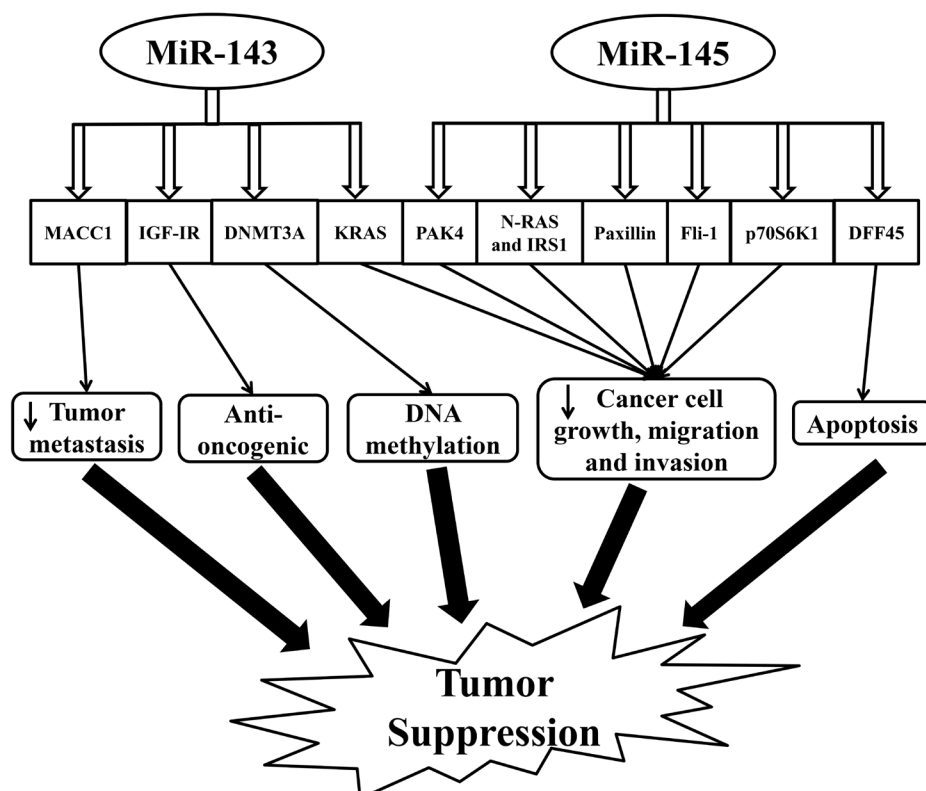


Figure 2: Schematic illustrating the tumor suppression effect regulated by miR-143 and miR-145 in colorectal cancer. Abbreviations: DNMT3A, DNA methyltransferases 3A; DFF45, DNA fragmentation factor-45; IGF-IR, insulin-like growth factor-I receptor; IRS1, insulin receptor substrate-1; KRAS, Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; MACC1, metastasis-associated in colon cancer-1; p70S6K1, phosphorylated 70-kDa ribosomal protein S6 kinase 1; PAK4, p-21 activated kinase 4.

responses and their aberrant expressions in the immune system are observed in cancers. Indeed, microRNA-related immunotherapy has recently been employed in colorectal cancer treatment.

More than half of the patients with colorectal cancer experience recurrence and metastasis after surgical resection. Sadly, conventional non-surgical treatment such as chemotherapy is ineffective against metastasis, and the poor prognosis further indicates the urge of developing novel therapeutics that improve clinical outcomes [112]. The immunomodulatory role of microRNAs is gradually recognized and investigated by multiple studies. MicroRNAs have been shown to mediate tumor immune escape by indirectly suppressing T cell activation and proliferation. For example, upregulated MiR-21 and miR-130b in advanced colorectal cancer can inhibit phosphatase and tensin homolog (*PTEN*; a tumor suppressor gene) expression, leading to programmed death ligand 1 (PD-L1) overexpression and immune evasion of colorectal cancer [112, 113]. MiR-124 has been shown to post-transcriptionally target signal transducer and activator of transcription 3 (STAT3), which is overly activated in each stage of colorectal cancer development and is associated with tumor-mediated immunosuppression [112, 114]. Accordingly, Zhang *et al.* observed reduced colorectal cancer cell survival and tumor growth *in vitro* and *in vivo*, respectively, when miR-124, a microRNA known to be downregulated in colorectal cancer, was re-introduced [114]. It is plausible to control inflammatory signaling pathways and immune responses *via* microRNA therapy, thereby decreasing the risk of colorectal tumorigenesis.

The development of microRNA-based treatments, including immunotherapy, remains challenging [110, 112, 115]. Although one single microRNA can regulate a broad set of genes simultaneously, allowing for effective targeting of heterogeneous cancer cells, it is likely to induce off-target side effects due to lack of specificity. The safe delivery and retention of exogenous microRNAs *in vivo* also pose difficulty in microRNA-based treatments [110, 115]. To date, no therapeutic manipulation of microRNAs has been applied in human patients with colorectal cancer; research is only at an experimental stage in either cell lines or animal models. Given the great significance of microRNAs as biomarkers that can be manipulated to reverse tumor progression, we cannot help speculating that a new therapeutic concept--a microRNA-based therapy--might be used in colorectal cancer in the near future. However, standardized microRNA measurement and analysis should be utilized to obtain valid prognostic and diagnostic microRNA profiles in colorectal cancer before their application in the clinical setting.

CONCLUSIONS

Accumulating evidence has significantly expanded

our understanding of microRNA in the pathogenesis of colorectal cancer in all critical progressions of tumorigenesis including cell proliferation, apoptosis, metastasis, and chemoresistance. However, we do not yet completely understand the biology of microRNAs in colorectal cancer development, as well as its association with oxidative stress. In addition, varied methods of handling and processing of microRNA yield inconsistent or incomparable results. It is therefore necessary to establish standardized microRNA protocols and analysis to obtain reliable data and accurately quantify microRNAs by developing a set of stable reference genes for each type of cancer. Besides all the unknowns and difficulties, microRNAs have demonstrated their potential as diagnostic biomarkers. Along with redox therapies targeting cancer cells, the development of personalized therapeutic targets utilizing microRNA for colorectal cancer is feasible. However, the aforementioned challenges should be addressed for the successful transition of microRNAs as prospective biomarkers from bench to clinical setting.

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CONFLICTS OF INTEREST

No conflicts of interest, financial or otherwise, are declared by the authors.

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